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Controlled Release of Aldicarb From Carboxymethylcellulese Microcapsules

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Sodium carboxymethyl cellulose was converted into microspheres by crosslinking with aluminum chloride. Various microsheres with different amounts of crosslinker, biopolymer of various concentrations and molecular weights, and with different pesticide (Aldicarb) contents and pesticide to polymer ratios were prepared. The pesticide encapsulation efficiencies and aldicarb release kinetics of the resultant microcapsules were investigated. It was possible to modify the release behaviour by varying the above parameters and to have drug release with half-lives longer than 100 hours in aqueous media. The release kinetics were described by first order and zero order kinetics.

Introduction

A major cause of man-made pollution is pesticides used for eradicating pests that attack human or livestock food sources. Man uses extensive quantities of these toxic chemicals to compensate for losses caused by evaporation, rain wast-out, or dispersion to unwanted regions due to wind and other factors. An approach quite intensively studied in the biomedical field for providing low but constant amounts of bioactive species (drugs, enzymes, etc.), is called controlled release, and is receiving attention because of growing data concerning the toxicity of excessive doses applied in the conventional way[1]. The approach involves release of the bioactive species according to a concentration gradient by diffusion through a matrix or a membrane and can be described by various release models. In the construction of these drug release systems in the biomedical field, biodegradable carriers are preferred since there is no need to remove the device from the body after completion of the therapy. This is both economical and risk free, and it spares the patient the pain of undergoing another operation. Controlled release systems constructed with degradable supports can be applied in the agricultural field for a different reason. The depleted drug depots that would normally

remain behind after a controlled release application constitutes a different kind of pollution. By using controlled release systems with biodegradable drug depots or supports, pollution caused by both excessive use of pesticides and depletion of the drug carrier material is prevented.

The ultimate aim of this study was to design a biodegradable and economical controlled relaase system for the pesticide aldicarb (2-methyl-2(methylthio)propionaldehyde O-(methylcarbamoly) oxime). It is a systemic pesticide used to control a variety of plant pests like nematodes, insects and mites, and is of special importance for cotton growers. It is a potential neurotoxicant and is known to exert its action through irreversible inhibition of the enzyme acetylcholine esterase.

The effectiveness of aldicarb, like that of any soil-applied pesticide, depends on its spatial distribution in the soil and its ability to reach the target organism in an adequate concentration for a certain minimum period of time. Therefore, adsorption and degradation have a pronounced effect on the behavior and effectiveness of it. A controlled release system is expected to significantly increase its effectiveness and decrease potential risks due to possible excessive use.

Sodium carboxymethyl cellulose is a water soluble polymer rendered hydrophilic by carboxymethylation. Its high water content makes it highly permeable and mechanically weak, which is advantageous for some uses due to enhanced degradability[2]. Its degradation by cellulases in nature makes it a potential candidate for various uses in which it can be made to replace polymers of petroleum origin. This is also important because polymers of petroleum origin are limited in stock and are non-degradable, making them a major cause of pollution. Thus carboxymethyl cellulose is a good candidate for use in the construction of a controlled release pesticide system.

It was therefore decided to construct the controlled release system using aldicarb as the pesticide and carboxymethylcellulose as the drug depot from which release will take place.

Materials and Methods

Carboxymethylcellulose sodium salt (NaCMC) low viscosity (purity > 99.5%; viscosity (4% in water, 25°C): 90-200 mPa.s; degree of substitution 0.70-0.85) was purchased from Fluka, AG (Switzerland). Carboxymethylcellulose sodium salt (NaCMC) high viscosity (viscosity (1% in water, 25°C 1500-3000 cps) was purchased from Sigma (USA).

Aluminium chloride (anhydrous) and sodium hydroxide were purchased from Merck, AG (Germany). Aldicarb, [2-methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl) oxime], was purified from a generous gift of Temik (15%(w/w) in aldicarb) from Mr. H. Kıroğlu (Rhone-Poulenc Tarım İlaçları Ltd, İstanbul, Turkey) by extraction and crystallization in diethyl ether.

Preparation of Aldicarb-Loaded Microspheres

The microspheres were prepared by using NaCMC as the main support material and aluminium chloride as the crosslinker using the experimental set-up presented earlier[3].

Aluminium chloride solutions (0.2M, 0.4M and 0.6M) were prepared and filtered in a vacuum.

Aqueous NaCMC solutions 2 and 3% (w/v) were prepared and centrifuged at 7000 rpm for 15 minutes and the supernatant was stored at 4°C until use.

For the preparation of the microcapsules, NaCMC solution (25 cm^3) was degassed, and introduced, dropwise using a peristaltic pump (Scientific Industries Inc., USA), into aluminium chloride solution (150 cm^3) while continuously stirring. Finely ground drug (sieved through Millipore stainless steel filter; pore

size 0.25 mm) was added to the polymer solution before preparation. They were then filtered, washed 5 times with fresh 200 cm^3 portions of distilled water, and dried in an airstream at room temperature.

Loading was defined as the amount of aldicarb (mg) contained in a milligram of dry microsphere (including CMC as well as the aldicarb).

Encapsulation efficiency was defined as the percent of the initial drug in the drug polymer mixture found in the microcapsules. The aldicarb amount used in these calculations was determined from the release data.

Release of Aldicarb

The release behavior of aldicarb-loaded microspheres were studied after placing the loaded microspheres (200 mg) in a continuous flow system (Figure 1) with a distilled water flow rate of 80 cm^3/h at room temperature. The amount of released aldicarb was determined at 246.5 nm using a UV-Vis spectrophotometer (Shimadzu UV-2100S, and UV-1201).

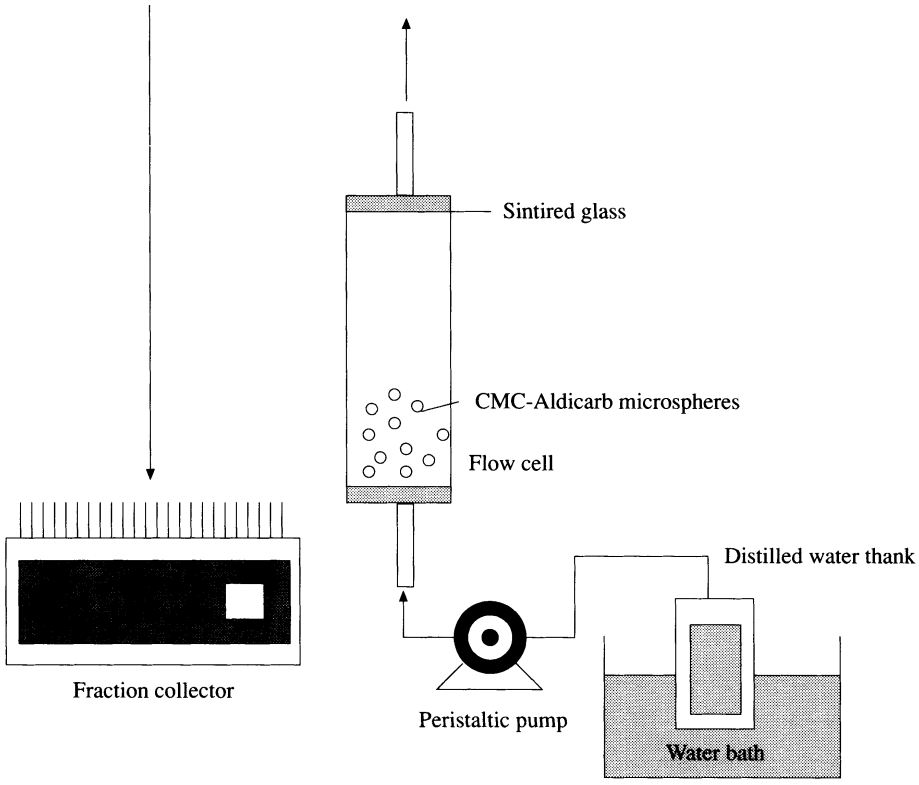

Figure 1. Continuous flow system for the release of aldicarb

Results and Discussion

The influence of molecular weight on microsphere properties can be observed when microspheres 1,3 and 5 are compared with microspheres 2, 4 and 6 (Table 1). It is observed that higher molecular weight leads to higher loading and higher encapsulation efficiency. This is expected because of the viscosity of the polymer solution used in the preparation of the microcapsules.

Table 1. Carboxymethylcellulose Microsphere Preparation Conditions

Sample Number	CMC Molecular Weight	CMC Concentration (%)	$AlCl_3$ Concentration (M)	Aldicarb (g)/ 50 mL CMC solution	Encapsulation (%)	Loading (mg ALD/200 mg microsphere)
1	LOW	2	0.2	0.50	17.33	15.28
2	HIGH	2	0.2	0.50	16.27	15.42
3	LOW	2	0.6	0.50	11.32	10.00
4	HIGH	2	0.6	0.50	28.21	24.18
5	LOW	2	0.4	0.50	29.24	24.19
6	HIGH	2	0.4	0.50	34.16	27.54
7	LOW	4	0.2	0.75	34.79	21.93
8	LOW	3	0.2	0.75	54.24	41.57
9	LOW	3	0.4	0.75	63.71	47.04
10	LOW	3	0.6	0.75	67.91	48.80

When the influence of the polymer to drug ratio is investigated, 1 and 8, 7 and 8, and 5 and 9 are to be compared, 1 and 8, and 5 and 9 have the same drug to polymer ratio, but in 8 and 9 the polymer is more concentrated and the loadings are higher. For some reason, 7 and 8 do not follow this pattern.

The effect of crosslinker concentration is observed when 2,6,4 or 1,5,3 are compared. In both cases, the microcapsules with the medium crosslinker concentration had the highest encapsulation efficiency and the highest loadings.

The release behaviour on the other hand yielded a different picture (Figures 2-4). On the whole it was observed that with a material normally used to cause the bursting of drug capsules, there was drug release in a continually flowing solvent system for about 100 hours with release of less than half the contents.

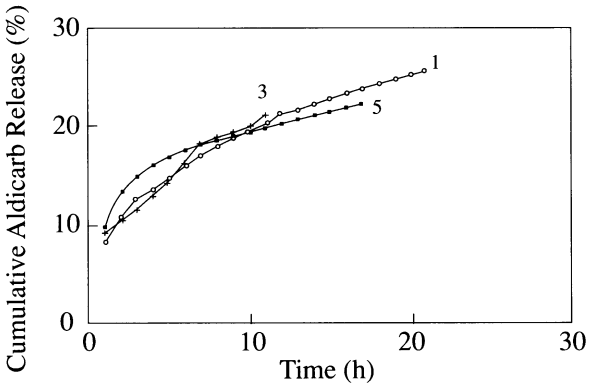

Figure 2. Cumulative release (%) behaviour of microspheres 1,3 and 5.

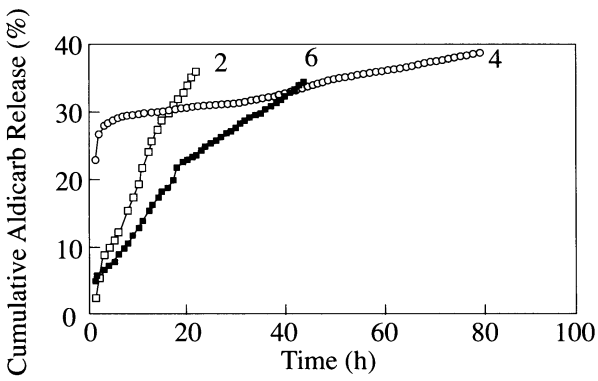

Figure 3. Cumulative release (%) behaviour of microspheres 2,4 and 6.

It was observed that when low molecular weight CMC was used, the release behaviour did not depend on the crosslinking degree and a basically first order release was observed (Figure 2). With the use of the higher molecular weight sample, the crosslinking degree had its influence and it was possible to observe releases which could be represented more by a zero order kinetics (Figure 3). In particular, microcapsules prepared with the highest crosslinking degree had a very slow release after an initial burst period. When the higher concentration CMC solutions with higher drug to polymer ratios were used, after the burst periods the release rates behaved according to their crosslinker contents (Figure 4).

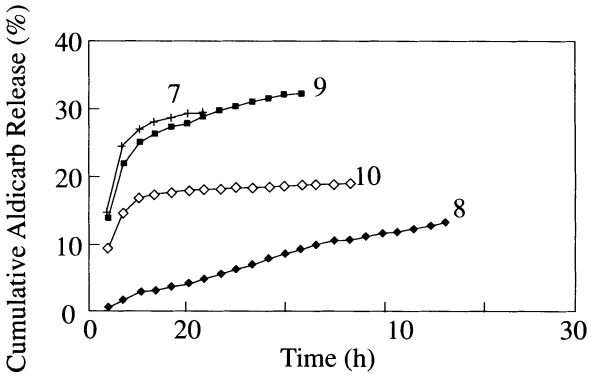

Figure 4. Cumulative release (%) behaviour of microspheres 7,8,9 and 10.

In these encapsulation efficiency and release studies, it was apparent that it was not easy to predict accurately the encapsulation efficiency or release behaviour from preparation conditions such as crosslinker contents or drug to polymer ratios, even through most of the time the expected results were obtained. The main reason for this lies in the fact that CMC is a polyelectrolyte which ionizes in the solution and that it solubility or chain conformation depends greatly on its degree of ionization. In media with low pH (such as when high crosslinker concentration is used) the polyelectrolyte is highly protonated and the chain coils upon itself, leading to a compact structure. Furthermore, the sites used for crosslinking are decreased. Thus, changing the crosslinker concentration has additional and counteracting effects other than what is expected from changed crosslinking degrees. In addition, a high crosslinker concentration leads to rapid crosslinking on the surface of the microcapsule, preventing the extension of crosslinkage inwards[3]. This was observed microscopically as a skin layer on the surface and a jelly-like interior. With lower crosslinker concentrations, a more uniform crosslinkage was observed.

A a result, it can be stated that in general it was possible to prepare microcapsules by crosslinking Na CMC with trivalent cations, and to modify their drug encapsulating and release capabilities by varying the crosslinker and polymer concentrations, polymer molecular weight, and drug to polymer ratio. The reasonably long drug release durations (a half-life of more than 100h with no. 4) makes them an appropriate choice for the release of pesticides in fields where they can be degraded upon depletion of their contents.

Acknowledgements

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